Multidisciplinary Journal of Horseed International University (MJHIU)
ISSN 2959-4154
Vol. 3, Issue 2, 2025
DOI: http://dx.doi.org/10.59336/6aw8yr31

**REVIEW ARTICLE**

# Neuroimmune Crosstalk in Neurodegenerative Diseases: Pathogenic Mechanisms and Therapeutic Potentials

Olayemi Oluwaseye Emmanuel[1*], Oyesola Olusoji Adebusoye[1], Sobowale Zainob Oluwaferanmi[1], Bamgbose Opeyemi Abel[2] and Anthony Elizabeth Chinenye[2]

*[1]Department of Physiology, Olabisi Onabanjo University, Ago-Iwoye, Nigeria; [2]Department of Anatomy, Olabisi Onabanjo University, Ago-Iwoye, Nigeria*

**Received:** June 25, 2025
**Accepted:** August 31, 2025
**Published:** September 15, 2025

**Abstract:** Neurodegenerative diseases such as Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis are increasingly understood as disorders of disrupted neuroimmune crosstalk. This review synthesizes recent advances on the bidirectional interactions between CNS glia and peripheral immune cells, emphasizing how dysregulated pathways—including NF-κB, NLRP3 inflammasome, and JAK/STAT signaling—drive chronic inflammation, synaptic dysfunction, and neuronal loss. This study integrates disease-specific mechanisms, from TREM2/CD33 dysfunction in Alzheimer's to α-synuclein–TLR signaling in Parkinson's and astrocyte–motor neuron toxicity in ALS. More so, this study highlights how targeting glial phenotypes, immune checkpoints, and the CNS–periphery axis—through CSF1R inhibitors, TREM2 agonists, astrocytic modulators, and microbiota-based strategies—may redefine disease modification. By uniting molecular insights with emerging biomarker-guided interventions, this review underscores the translational potential of neuroimmune modulation in restoring CNS homeostasis.

**Keywords:** Neuroinflammation, Microglia, Astrocytes, Neurodegeneration, Immune signaling

## 1. INTRODUCTION

Neurodegenerative diseases are progressive disorders characterized by the selective loss of neurons and synaptic dysfunction in the central nervous system (CNS). These conditions represent a growing global health burden, with neurodegeneration-associated mortality and disability rates projected to rise due to aging populations (Feigin *et al.,* 2020). Despite extensive research, effective disease-modifying therapies remain elusive, largely due to the complex etiology of neurodegeneration, which encompasses not only neuronal loss but also dysregulated immune responses within the CNS.

Recent advances in neuroimmunology have shifted the paradigm from a neuron-centric view of neurodegeneration to one that recognizes the integral role of immune cells in both maintaining CNS homeostasis and driving neuropathology (Prinz *et al.,* 2021). Neuroimmune crosstalk describes the bidirectional, context-dependent communication between neurons and glial cells, as well as interactions between the CNS and peripheral immune signals. Microglia—the brain's resident macrophages—respond to injury and disease by transitioning into reactive states, releasing cytokines such as TNF-α, IL-1β, and IL-6, which

---

**Correspondence should be addressed to Department of Physiology, Olabisi Onabanjo University, Ago-Iwoye, Nigeria; Tel: +2349060234406; E-mail: Olayemi.oluwaseye@oouagoiwoye.edu.ng; Orchid: https://orcid.org/0009-0009-1764-608X;*

influence neuronal survival and synaptic function (Colonna & Butovsky, 2017). Astrocytes, once considered passive support cells, now are understood to actively modulate synaptic transmission, blood-brain barrier (BBB) permeability, and neuroinflammatory responses (Sofroniew, 2020).

Acute neuroinflammation, often seen after injury or infection, may initially serve protective roles by clearing debris and promoting tissue repair. However, chronic neuroinflammation—marked by sustained glial activation, persistent cytokine release, and failure to resolve the immune response—has been implicated in neuronal degeneration and disease progression (Luz *et al.,* 2024). In diseases like Alzheimer's Disease (AD), Parkinson's Disease (PD), and Amyotrophic Lateral Sclerosis (ALS), prolonged inflammatory signaling not only exacerbates neuronal dysfunction but also alters glial cell phenotypes, creating a toxic milieu that perpetuates tissue damage.

This review aims to dissect the molecular and cellular mechanisms by which neuroimmune crosstalk contributes to neurodegeneration by examining how glial activation, cytokine signaling, and immune dysregulation mediate neuronal injury; exploring molecular pathways such as NF-κB, NLRP3 inflammasome, and JAK/STAT that orchestrate neuroinflammatory responses; and evaluating emerging immunomodulatory strategies—ranging from microglial reprogramming to peripheral cytokine inhibition—as potential therapeutic avenues to halt or reverse neurodegenerative processes. This review provides integrative focus on linking disease-specific molecular mechanisms to convergent therapeutic strategies. By highlighting how diverse immune pathways intersect across Alzheimer's, Parkinson's, and ALS, it provides a unifying framework that underscores the translational potential of neuroimmune modulation for disease modification.

## 2. NEUROIMMUNE CELLS AND THEIR PHYSIOLOGICAL ROLES

### 2.1. Microglia in CNS Surveillance and Synaptic Pruning

Microglia, the principal immune effector cells of the central nervous system (CNS), originate from yolk sac progenitors and colonize the brain early in embryogenesis (Bennett & Bennett, 2020). In the healthy adult brain, microglia continuously survey the microenvironment with highly motile processes, maintaining tissue homeostasis by detecting perturbations in neuronal activity, synaptic integrity, and extracellular composition (Cole *et al.,* 2020). This surveillance role is essential for synaptic pruning—a developmental process in which excess or weak synapses are eliminated to optimize neural circuitry. Microglia mediate this *via* complement receptor signaling, particularly through C1q and C3 tagging of synapses, which are then phagocytosed (Mendoza-Romero *et al.,* 2025). Beyond development, microglia also contribute to adult synaptic plasticity and learning by modulating synapse turnover in response to activity patterns (Woodburn *et al.,* 2025).

Historically, microglial activation was described using a binary M1/M2 paradigm, wherein M1 referred to pro-inflammatory, neurotoxic phenotypes, and M2 described anti-inflammatory, reparative states. However, this dichotomy is now considered overly simplistic and inconsistent with transcriptomic and proteomic evidence from in vivo studies (Carvalho, 2021). Instead, microglial activation is now conceptualized as a spectrum of context-dependent phenotypes shaped by local cues, developmental stage, and disease context. Disease-associated microglia (DAM) found in Alzheimer's disease exhibit a transcriptional profile distinct from classical M1/M2 polarization, including upregulation of Trem2, Apoe, and Tyrobp (Keren-Shaul *et al.,* 2017). These cells may initially serve protective roles by clearing amyloid-beta (Aβ), but their sustained activation can contribute to chronic neuroinflammation and synaptic dysfunction.

### 2.2. Astrocytes and Tripartite Synapse Regulation

Astrocytes, the most abundant glial cells in the CNS, perform essential homeostatic and neuromodulatory functions that extend beyond passive support. One of their pivotal roles is in the regulation of the tripartite synapse, a conceptual model in which astrocytic processes closely ensheath pre- and postsynaptic terminals to modulate synaptic transmission and plasticity (Aleksejenko & Heller, 2021). Astrocytes actively sense synaptic activity *via* a repertoire of neurotransmitter receptors and transporters, and in turn, release gliotransmitters such as glutamate, D-serine, and ATP, thereby influencing synaptic efficacy and neuronal excitability (Lim *et al.,* 2021).

At the molecular level, astrocytes are critical for neurotransmitter recycling—particularly glutamate. They express high-affinity excitatory amino acid transporters (EAAT1/GLAST and EAAT2/GLT-1), which rapidly clear extracellular glutamate, preventing excitotoxicity and preserving synaptic fidelity (Todd & Hardingham, 2020). Astrocytes also contribute to potassium ion ($K^+$) buffering through inwardly rectifying potassium channels (Kir4.1), maintaining the ionic balance required for proper neuronal signaling (Verkhratsky *et al.,* 2023). Furthermore, they regulate cerebral blood flow and maintain the blood-brain barrier (BBB) *via* endfeet processes that secrete vasoactive substances and modulate endothelial tight junction integrity (García-Salvador *et al.,* 2020).

Upon CNS injury or disease, astrocytes undergo a spectrum of morphological and molecular changes known as reactive astrogliosis. This process is regulated by pathways including STAT3, NF-κB, and JAK-STAT, leading to upregulation of glial fibrillary acidic protein (GFAP), cellular hypertrophy, and altered gene expression profiles (Linnerbauer *et al.,* 2020). While moderate astrogliosis can be neuroprotective—limiting lesion spread, repairing the BBB, and promoting debris clearance—chronic or severe reactivity may exacerbate neuronal injury. For instance, reactive astrocytes may downregulate glutamate transporters, contribute to inflammatory cytokine release, or form glial scars that hinder axonal regeneration (Matusova *et al.,* 2023; Li *et al.,* 2023).

## 3. NEUROINFLAMMATION IN NEURODEGENERATIVE DISORDERS

Neuroinflammation is a shared pathological hallmark across major neurodegenerative diseases, characterized by the sustained activation of glial cells and dysregulation of cytokine signaling. In Alzheimer's Disease (AD), microglia are among the earliest responders to amyloid-β (Aβ) deposition. Receptors such as TREM2 and CD33 critically shape microglial function: TREM2 facilitates Aβ clearance and supports neuroprotection, while CD33 inhibits phagocytosis and enhances inflammatory gene expression (Hou *et al.,* 2022; Griciuc *et al.,* 2020). Genetic variants in both receptors confer strong AD risk, underscoring their pathogenic relevance. Aβ also activates the NLRP3 inflammasome, amplifying IL-1β signaling, which disrupts synaptic plasticity and neurotransmission (Zhang *et al.,* 2020).

In PD, misfolded α-synuclein acts as a damage-associated molecular pattern (DAMP) that engages TLR2/4 on microglia, triggering NF-κB–mediated inflammatory responses and dopaminergic neuron injury (Xia *et al.,* 2021; Leńska-Mieciek *et al.,* 2023). Astrocytes exposed to α-synuclein aggregates adopt a neurotoxic A1 phenotype, amplifying neuronal stress (Yun *et al.,* 2018). Peripheral immune signals reinforce central inflammation: circulating TNF-α, IL-1β, and IL-6 correlate with disease severity and cross the blood–brain barrier to activate glia (Zimmermann & Brockmann, 2022). Infiltrating T cells further contribute to neurodegeneration through cytotoxicity and cytokine release (Cebrián *et al.,* 2014). Genetic risk factors (*e.g.,* LRRK2 mutations) and gut microbiota dysbiosis link systemic immune changes with central pathology (Cookson, 2017; Yang *et al.,* 2019).

ALS pathology involves motor neuron loss compounded by glial and peripheral immune dysregulation. Mutant SOD1 aggregates activate microglia through pattern-recognition receptors, inducing a neurotoxic phenotype characterized by iNOS and proinflammatory cytokine release (Ramírez *et al.,* 2022). Astrocytes also acquire toxic gain-of-function properties, releasing prostaglandin D2, oxidative metabolites, and cytokines that selectively impair motor neurons *via* non-cell-autonomous mechanisms (Gomes *et al.,* 2022). Elevated peripheral cytokines (*e.g.,* IL-6, TNF-α) correlate with disease progression (Hu *et al.,* 2017), while T cell infiltration shapes outcomes—Tregs are protective, whereas cytotoxic T cells exacerbate degeneration (Beers *et al.,* 2011). Additional vulnerability arises from oligodendrocyte dysfunction, which limits metabolic support to motor neurons (Philips & Rothstein, 2014).

## 4. MOLECULAR SIGNALING PATHWAYS IN NEUROIMMUNE ACTIVATION

The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway is a central mediator of inflammation in the central nervous system (CNS). It operates through two principal arms:

the canonical (classical) and non-canonical pathways. The canonical pathway, typically triggered by pattern recognition receptors such as toll-like receptors (TLRs), leads to the degradation of IκB and nuclear translocation of the p65/p50 dimer, activating transcription of genes encoding pro-inflammatory cytokines (*e.g.,* TNF-α, IL-6), chemokines, and adhesion molecules (Liu *et al.,* 2017). In contrast, the non-canonical pathway involves NF-κB–inducing kinase (NIK) and p52/RelB complexes and is associated with more sustained inflammatory responses. In glial cells, persistent NF-κB activation shifts microglia and astrocytes toward neurotoxic phenotypes, contributing to synaptic dysfunction, neuronal apoptosis, and blood–brain barrier breakdown (Li *et al.,* 2020). Thus, NF-κB serves as both a sensor and amplifier of neuroinflammation.

The NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome is a multi-protein complex that assembles in response to danger signals such as amyloid-β, α-synuclein, or reactive oxygen species. In microglia, activation of NLRP3 leads to oligomerization with ASC and pro-caspase-1, resulting in caspase-1 activation and maturation of interleukin-1β (IL-1β) and interleukin-18 (IL-18) (Heneka *et al.,* 2018). Chronic activation of the NLRP3 inflammasome contributes to sustained neuroinflammation in Alzheimer’s and Parkinson’s diseases by perpetuating cytokine release and glial priming. Inhibiting NLRP3—pharmacologically (*e.g.,* MCC950) or genetically—has shown promise in reducing pathology and cognitive decline in preclinical AD models (Stancu *et al.,* 2022). This makes the inflammasome a compelling therapeutic target.

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway transmits signals from cytokine receptors (*e.g.,* IL-6R, IFNGR) to the nucleus, resulting in transcription of inflammatory mediators and immune regulatory genes. In glial cells, STAT3 activation enhances astrocytic reactivity and scar formation, while also contributing to both protective and deleterious outcomes depending on context (Ben Haim *et al.,* 2015). Similarly, the mitogen-activated protein kinase (MAPK) pathways—including p38, JNK, and ERK—regulate cellular responses to stress and cytokines. Activation of p38 MAPK in microglia promotes the release of TNF-α and IL-1β, while ERK signaling is associated with microglial proliferation and migration (Lin *et al.,* 2022). Cross-talk between JAK/STAT and MAPK pathways fine-tunes glial activation states and the balance between neuroprotection and neurotoxicity.

### 5.1. Microglia Modulation Strategies

Microglial plasticity renders them attractive targets for therapeutic intervention. Inhibitors of colony-stimulating factor 1 receptor (CSF1R), such as PLX5622, selectively deplete microglia or modulate their activation states without affecting other CNS cells (Barca *et al.,* 2021). While microglial depletion shows neuroprotective effects in certain models, chronic suppression may impair synaptic maintenance and immune surveillance, necessitating a nuanced approach.

An alternative strategy involves enhancing microglial reparative functions *via* TREM2 (triggering receptor expressed on myeloid cells 2) activation. TREM2 agonist antibodies have shown promise in promoting phagocytic clearance of amyloid plaques and limiting inflammation in Alzheimer’s disease models (Wang *et al.,* 2020).

## 5. THERAPEUTIC TARGETING OF NEUROIMMUNE PATHWAYS

### 5.2. Astrocyte-Specific Therapies

Therapeutics targeting astrocytes aim to restore their homeostatic functions while preventing toxic reactivity. The A1/A2 paradigm, though oversimplified, serves as a framework to differentiate neurotoxic versus neuroprotective astrocyte responses (Liddelow *et al.,* 2017). Efforts to inhibit the transformation to A1 phenotypes using cytokine blockers (*e.g.,* IL-1α, TNF-α neutralization) or by modulating NF-κB/STAT3 signaling show potential. Gene therapy approaches, such as CRISPR-Cas9-mediated correction of astrocyte dysfunction or delivery of anti-inflammatory microRNAs, are also under investigation to reprogram astrocyte phenotypes toward support of neuronal survival Fig. (**1**).

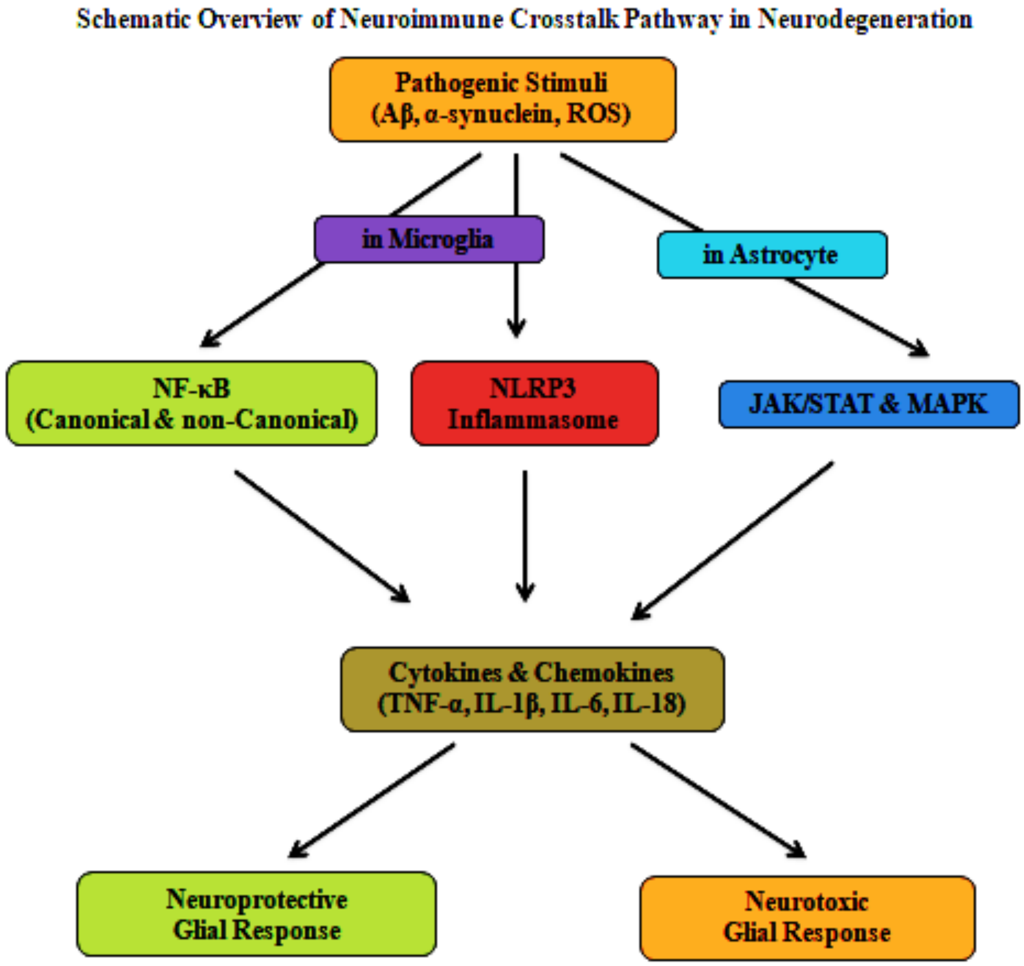

**Figure 1.** Schematic overview of the NF-κB, NLRP3, and JAK/STAT–MAPK pathways, illustrating how pathogenic stimuli (Aβ, α-synuclein, ROS) activate glial signaling, leading to cytokine release and divergent neuroprotective versus neurotoxic outcomes.

## 5.3. Peripheral Immunomodulation

Given the permeability of the blood–brain barrier (BBB) in neurodegeneration, peripheral immune cells and cytokines contribute significantly to CNS inflammation. Anti-cytokine therapies, such as IL-1β inhibitors (*e.g.,* canakinumab) and TNF-α blockers (*e.g.,* etanercept), have shown mixed results in neurodegenerative conditions but remain a focus in trials for Alzheimer's and Parkinson's diseases (Decourt *et al.,* 2017). BBB-protective agents—such as sphingosine-1-phosphate receptor modulators (*e.g.,* fingolimod)—reduce lymphocyte trafficking and microglial activation, offering a means to mitigate immune infiltration and chronic inflammation.

## 5.4. Regenerative Interventions and Neuroimmune Support

Mesenchymal stem cells (MSCs) and their secreted exosomes have demonstrated capacity to modulate microglial and astrocytic activation, reduce cytokine production, and enhance neurotrophic support (Shah *et al.,* 2024). Their anti-inflammatory and regenerative potential makes them a strong candidate for future neuroimmune therapies. Lifestyle interventions also influence neuroinflammation. Dietary polyphenols, gut microbiota modulation, and aerobic exercise have been shown to suppress microglial activation and improve cognitive function *via* systemic immune changes and CNS signaling pathways (Cryan *et al.,* 2019). These approaches underscore the role of systemic health in modulating neuroimmune balance (Table **1**).

**Table 1. Therapeutic strategies targeting neuroimmune interactions in neurodegenerative diseases.**

| Strategy | Approach | Examples/Agents | Therapeutic Potential | Limitations/Challenges |
|---|---|---|---|---|
| Microglia modulation | Depletion or reprogramming of microglia | CSF1R inhibitors (PLX5622) (Barca *et al.,* 2021); TREM2 agonist antibodies (Wang *et al.,* 2020) | Reduces neurotoxic microglial activation; enhances phagocytosis and amyloid clearance | Chronic depletion may impair synaptic maintenance and immune surveillance |
| Astrocyte-specific therapies | Block toxic A1 conversion; enhance protective functions | Cytokine blockers (IL-1α, TNF-α neutralization); NF-κB/STAT3 modulation; gene therapy (CRISPR, anti-inflammatory miRNAs) (Liddelow *et al.,* 2017) | Restores astrocytic support of neurons; reduces toxic reactivity | Complexity of A1/A2 phenotypes; delivery challenges for gene therapy |
| Peripheral immunomodulation | Target peripheral cytokines and BBB dysfunction | IL-1β inhibitors (canakinumab), TNF-α blockers (etanercept) (Decourt *et al.,* 2017); S1P modulators (fingolimod) | Reduces peripheral inflammation and immune infiltration; protects BBB integrity | Mixed efficacy in clinical trials; systemic immunosuppression risks |
| Regenerative & supportive interventions | Stem cell therapy; lifestyle modification | MSCs and exosomes (Shah *et al.,* 2024); dietary polyphenols, microbiota modulation, aerobic exercise (Cryan *et al.,* 2019) | Anti-inflammatory and neurotrophic effects; promotes repair and resilience | Variable efficacy; translational and standardization challenges |

## FUTURE DIRECTIONS AND CONCLUSION

The evolving understanding of neuroimmune crosstalk has fundamentally reshaped the conceptualization of neurodegenerative diseases, placing glial cells and immune signaling at the core of both pathogenic mechanisms and therapeutic strategies. Future research is increasingly directed toward high-resolution approaches such as single-cell and spatial transcriptomics, which are uncovering the molecular heterogeneity and dynamic states of microglia and astrocytes in diseased brains. This cellular diversity underscores the need for precision immunotherapies tailored to disease stage, region-specific pathologies, and individual immune signatures. Notably, strategies targeting CSF1R or activating TREM2 are emerging as promising methods to reprogram dysfunctional microglia. Additionally, peripheral immune influences, especially those arising from gut microbiota and systemic inflammation, are gaining attention as modulators of CNS immunity, with dietary interventions and microbiota-derived metabolites offering novel therapeutic leverage points. In parallel, efforts are underway to develop robust biomarkers—such as PET imaging of TSPO or fluid measures like soluble TREM2 and GFAP—to enable early diagnosis and monitor treatment efficacy. Stem cell-based therapies and engineered exosomes are also at the forefront of regenerative neuroimmunology, offering targeted delivery of trophic and anti-inflammatory factors across the blood–brain barrier.

In conclusion, neurodegenerative diseases such as Alzheimer's, Parkinson’s, and ALS should be viewed not solely as neuronal disorders but as complex syndromes of dysfunctional neuroimmune communication. Targeting glial activation states, inflammatory signaling cascades, and the CNS–periphery immune axis represents a multifaceted therapeutic frontier. Moving forward, interdisciplinary approaches integrating molecular neuroscience, systems immunology, and translational medicine are essential to realize the potential of neuroimmune modulation for neuroprotection, repair, and functional recovery.

## AUTHORS' CONTRIBUTIONS

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

## CONSENT FOR PUBLICATION

Not applicable.

## FUNDING

None.

## CONFLICT OF INTEREST

The author confirms that this article's content has no conflict of interest.

## ACKNOWLEDGEMENTS

Declared none.

## REFERENCES

Aleksejenko, N., & Heller, J. P. (2021). Super-resolution imaging to reveal the nanostructure of tripartite synapses. Neuronal signaling, 5(4), NS20210003. https://doi.org/10.1042/NS20210003

Barca, C., Foray, C., Hermann, S., Herrlinger, U., Remory, I., Laoui, D., Schäfers, M., Grauer, O. M., Zinnhardt, B., & Jacobs, A. H. (2021). The Colony Stimulating Factor-1 Receptor (CSF-1R)-Mediated Regulation of Microglia/Macrophages as a Target for Neurological Disorders (Glioma, Stroke). Frontiers in immunology, 12, 787307. https://doi.org/10.3389/fimmu.2021.787307

Beers, D. R., Zhao, W., Liao, B., Kano, O., Wang, J., Huang, A., Appel, S. H., & Henkel, J. S. (2011). Neuroinflammation modulates distinct regional and temporal clinical responses in ALS mice. *Brain, behavior, and immunity*, *25*(5), 1025–1035. https://doi.org/10.1016/j.bbi.2010.12.008

Ben Haim, L., Ceyzériat, K., Carrillo-de Sauvage, M. A., Aubry, F., Auregan, G., Guillermier, M., Ruiz, M., Petit, F., Houitte, D., Faivre, E., Vandesquille, M., Aron-Badin, R., Dhenain, M., Déglon, N., Hantraye, P., Brouillet, E., Bonvento, G., & Escartin, C. (2015). The JAK/STAT3 pathway is a common inducer of astrocyte reactivity in Alzheimer's and Huntington's diseases. The Journal of neuroscience : the official journal of the Society for Neuroscience, 35(6), 2817–2829. https://doi.org/10.1523/JNEUROSCI.3516-14.2015

Bennett, M. L., & Bennett, F. C. (2020). The influence of environment and origin on brain resident macrophages and implications for therapy. Nature neuroscience, 23(2), 157–166. https://doi.org/10.1038/s41593-019-0545-6

Carvalho, K. (2021). Gene Expression and Chromatin Dynamics During Macrophage Polarization in Health and Disease. University of California, Irvine.

Cebrián, C., Zucca, F. A., Mauri, P., Steinbeck, J. A., Studer, L., Scherzer, C. R., Kanter, E., Budhu, S., Mandelbaum, J., Vonsattel, J. P., Zecca, L., Loike, J. D., & Sulzer, D. (2014). MHC-I expression renders catecholaminergic neurons susceptible to T-cell-mediated degeneration. *Nature communications*, *5*, 3633. https://doi.org/10.1038/ncomms4633

Cole, A. P., Hoffmeyer, E., Chetty, S. L., Cruz-Cruz, J., Hamrick, F., Youssef, O., Cheshier, S., & Mitra, S. S. (2020). Microglia in the Brain Tumor Microenvironment. Advances in experimental medicine and biology, 1273, 197–208. https://doi.org/10.1007/978-3-030-49270-0_11

Colonna, M., & Butovsky, O. (2017). Microglia Function in the Central Nervous System During Health and Neurodegeneration. Annual review of immunology, 35, 441–468. https://doi.org/10.1146/annurev-immunol-051116-052358

Cookson M. R. (2017). Mechanisms of Mutant LRRK2 Neurodegeneration. *Advances in neurobiology*, *14*, 227–239. https://doi.org/10.1007/978-3-319-49969-7_12

Cryan, J. F., O'Riordan, K. J., Cowan, C. S. M., Sandhu, K. V., Bastiaanssen, T. F. S., Boehme, M., Codagnone, M. G., Cussotto, S., Fulling, C., Golubeva, A. V., Guzzetta, K. E., Jaggar, M., Long-Smith, C. M., Lyte, J. M., Martin, J. A., Molinero-Perez, A., Moloney, G., Morelli, E., Morillas, E., O'Connor, R., … Dinan, T. G. (2019). The Microbiota-Gut-Brain Axis. Physiological reviews, 99(4), 1877–2013. https://doi.org/10.1152/physrev.00018.2018

Decourt, B., Lahiri, D. K., & Sabbagh, M. N. (2017). Targeting Tumor Necrosis Factor Alpha for Alzheimer's Disease. Current Alzheimer research, 14(4), 412–425. https://doi.org/10.2174/1567205013666160930110551

García-Salvador, A., Domínguez-Monedero, A., Gómez-Fernández, P., García-Bilbao, A., Carregal-Romero, S., Castilla, J., & Goñi-de-Cerio, F. (2020). Evaluation of the Influence of Astrocytes on In Vitro Blood-Brain Barrier Models. Alternatives to laboratory animals : ATLA, 48(4), 184–200. https://doi.org/10.1177/0261192920966954

GBD 2016 Neurology Collaborators (2019). Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet. Neurology, 18(5), 459–480. https://doi.org/10.1016/S1474-4422(18)30499-X

Gomes, C., Sequeira, C., Likhite, S., Dennys, C. N., Kolb, S. J., Shaw, P. J., Vaz, A. R., Kaspar, B. K., Meyer, K., & Brites, D. (2022). Neurotoxic Astrocytes Directly Converted from Sporadic and Familial ALS Patient Fibroblasts Reveal Signature Diversities and miR-146a Theragnostic Potential in Specific Subtypes. Cells, 11(7), 1186. https://doi.org/10.3390/cells11071186

Griciuc, A., Federico, A. N., Natasan, J., Forte, A. M., McGinty, D., Nguyen, H., Volak, A., LeRoy, S., Gandhi, S., Lerner, E. P., Hudry, E., Tanzi, R. E., & Maguire, C. A. (2020). Gene therapy for Alzheimer's disease targeting CD33 reduces amyloid beta accumulation and neuroinflammation. Human molecular genetics, 29(17), 2920–2935. https://doi.org/10.1093/hmg/ddaa179

Heneka, M. T., McManus, R. M., & Latz, E. (2018). Inflammasome signalling in brain function and neurodegenerative disease. Nature reviews. Neuroscience, 19(10), 610–621. https://doi.org/10.1038/s41583-018-0055-7

Hou, J., Chen, Y., Grajales-Reyes, G., & Colonna, M. (2022). TREM2 dependent and independent functions of microglia in Alzheimer's disease. Molecular neurodegeneration, 17(1), 84. https://doi.org/10.1186/s13024-022-00588-y

Hu, Y., Cao, C., Qin, X. Y., Yu, Y., Yuan, J., Zhao, Y., & Cheng, Y. (2017). Increased peripheral blood inflammatory cytokine levels in amyotrophic lateral sclerosis: a meta-analysis study. *Scientific reports*, *7*(1), 9094. https://doi.org/10.1038/s41598-017-09097-1

Keren-Shaul, H., Spinrad, A., Weiner, A., Matcovitch-Natan, O., Dvir-Szternfeld, R., Ulland, T. K., David, E., Baruch, K., Lara-Astaiso, D., Toth, B., Itzkovitz, S., Colonna, M., Schwartz, M., & Amit, I. (2017). A Unique Microglia Type Associated with Restricting Development of Alzheimer's Disease. Cell, 169(7), 1276–1290.e17. https://doi.org/10.1016/j.cell.2017.05.018

Leńska-Mieciek, M., Madetko-Alster, N., Alster, P., Królicki, L., Fiszer, U., & Koziorowski, D. (2023). Inflammation in multiple system atrophy. Frontiers in immunology, 14, 1214677. https://doi.org/10.3389/fimmu.2023.1214677

Li, B., Chang, X., Liang, X., Liu, T., Shen, Y., Zhang, Q., Yang, X., Lyu, Y., Liu, L., Guo, J., Wu, M., Gao, Y., Yan, X., Wang, T., Zhang, W., Qiu, Y., & Zheng, J. (2023). The role of reactive astrocytes in neurotoxicity induced by ultrafine particulate matter. The Science of the total environment, 867, 161416. https://doi.org/10.1016/j.scitotenv.2023.161416

Li, X., Huang, L., Liu, G., Fan, W., Li, B., Liu, R., Wang, Z., Fan, Q., Xiao, W., Li, Y., & Fang, W. (2020). Ginkgo diterpene lactones inhibit cerebral ischemia/reperfusion induced inflammatory response in astrocytes *via* TLR4/NF-κB pathway in rats. Journal of ethnopharmacology, 249, 112365. https://doi.org/10.1016/j.jep.2019.112365

Liddelow, S. A., Guttenplan, K. A., Clarke, L. E., Bennett, F. C., Bohlen, C. J., Schirmer, L., Bennett, M. L., Münch, A. E., Chung, W. S., Peterson, T. C., Wilton, D. K., Frouin, A., Napier, B. A., Panicker, N., Kumar, M., Buckwalter, M. S., Rowitch, D. H., Dawson, V. L., Dawson, T. M., Stevens, B., … Barres, B. A. (2017). Neurotoxic reactive astrocytes are induced by activated microglia. Nature, 541(7638), 481–487. https://doi.org/10.1038/nature21029

Lim, D., Semyanov, A., Genazzani, A., & Verkhratsky, A. (2021). Calcium signaling in neuroglia. International review of cell and molecular biology, 362, 1–53. https://doi.org/10.1016/bs.ircmb.2021.01.003

Lin, H., Dixon, S. G., Hu, W., Hamlett, E. D., Jin, J., Ergul, A., & Wang, G. Y. (2022). p38 MAPK Is a Major Regulator of Amyloid Beta-Induced IL-6 Expression in Human Microglia. Molecular neurobiology, 59(9), 5284–5298. https://doi.org/10.1007/s12035-022-02909-0

Linnerbauer, M., Wheeler, M. A., & Quintana, F. J. (2020). Astrocyte Crosstalk in CNS Inflammation. Neuron, 108(4), 608–622. https://doi.org/10.1016/j.neuron.2020.08.012

Liu, T., Zhang, L., Joo, D., & Sun, S. C. (2017). NF-κB signaling in inflammation. Signal transduction and targeted therapy, 2, 17023–. https://doi.org/10.1038/sigtrans.2017.23

Luz, I. S., Takaya, R., Ribeiro, D. G., Castro, M. S., & Fontes, W. (2024). Proteomics: Unraveling the Cross Talk Between Innate Immunity and Disease Pathophysiology, Diagnostics, and Treatment Options. Advances in experimental medicine and biology, 1443, 221–242. https://doi.org/10.1007/978-3-031-50624-6_12

Matusova, Z., Hol, E. M., Pekny, M., Kubista, M., & Valihrach, L. (2023). Reactive astrogliosis in the era of single-cell transcriptomics. Frontiers in cellular neuroscience, 17, 1173200. https://doi.org/10.3389/fncel.2023.1173200

Mendoza-Romero, H. N., Biddinger, J. E., Bedenbaugh, M. N., & Simerly, R. (2025). Microglia are required for developmental specification of AgRP innervation in the hypothalamus of offspring exposed to maternal high-fat diet during lactation. eLife, 13, RP101391. https://doi.org/10.7554/eLife.101391

Philips, T., & Rothstein, J. D. (2017). Oligodendroglia: metabolic supporters of neurons. *The Journal of clinical investigation*, *127*(9), 3271–3280. https://doi.org/10.1172/JCI90610

Prinz, M., Masuda, T., Wheeler, M. A., & Quintana, F. J. (2021). Microglia and Central Nervous System-Associated Macrophages-From Origin to Disease Modulation. Annual review of immunology, 39, 251–277. https://doi.org/10.1146/annurev-immunol-093019-110159

Ramirez, A. I., de Hoz, R., Rojas, P., & Salazar, J. J. (2022). Amyotrophic lateral sclerosis, a neurodegenerative motor neuron disease with retinal involvement. Neural regeneration research, 17(5), 1011–1012. https://doi.org/10.4103/1673-5374.324841

Shah, S., Mansour, H. M., Aguilar, T. M., & Lucke-Wold, B. (2024). Mesenchymal Stem Cell-Derived Exosomes as a Neuroregeneration Treatment for Alzheimer's Disease. Biomedicines, 12(9), 2113. https://doi.org/10.3390/biomedicines12092113

Sofroniew M. V. (2020). Astrocyte Reactivity: Subtypes, States, and Functions in CNS Innate Immunity. Trends in immunology, 41(9), 758–770. https://doi.org/10.1016/j.it.2020.07.004

Sommer, A., Marxreiter, F., Krach, F., Fadler, T., Grosch, J., Maroni, M., Graef, D., Eberhardt, E., Riemenschneider, M. J., Yeo, G. W., Kohl, Z., Xiang, W., Gage, F. H., Winkler, J., Prots, I., & Winner, B. (2018). Th17 Lymphocytes Induce Neuronal Cell Death in a Human iPSC-Based Model of Parkinson's Disease. *Cell stem cell*, *23*(1), 123–131.e6. https://doi.org/10.1016/j.stem.2018.06.015

Stancu, I. C., Lodder, C., Botella Lucena, P., Vanherle, S., Gutiérrez de Ravé, M., Terwel, D., Bottelbergs, A., & Dewachter, I. (2022). The NLRP3 inflammasome modulates tau pathology and neurodegeneration in a tauopathy model. Glia, 70(6), 1117–1132. https://doi.org/10.1002/glia.24160

Todd, A. C., & Hardingham, G. E. (2020). The Regulation of Astrocytic Glutamate Transporters in Health and Neurodegenerative Diseases. International journal of molecular sciences, 21(24), 9607. https://doi.org/10.3390/ijms21249607

Verkhratsky, A., Butt, A., Li, B., Illes, P., Zorec, R., Semyanov, A., Tang, Y., & Sofroniew, M. V. (2023). Astrocytes in human central nervous system diseases: a frontier for new therapies. Signal transduction and targeted therapy, 8(1), 396. https://doi.org/10.1038/s41392-023-01628-9

Wang, S., Mustafa, M., Yuede, C. M., Salazar, S. V., Kong, P., Long, H., Ward, M., Siddiqui, O., Paul, R., Gilfillan, S., Ibrahim, A., Rhinn, H., Tassi, I., Rosenthal, A., Schwabe, T., & Colonna, M. (2020). Anti-human TREM2 induces microglia proliferation and reduces pathology in an Alzheimer's disease model. The Journal of experimental medicine, 217(9), e20200785. https://doi.org/10.1084/jem.20200785

Woodburn, S. C., Kuhn, A., Dadosky, D. T., Mueller, E., Bollinger, J. L., Gonzalez, R. M. S., ... & Wohleb, E. S. (2025). Microglial brain-derived neurotrophic factor (BDNF) supports the behavioral and synaptogenic effects of ketamine. bioRxiv, 2025-05.

Xia, Y., Zhang, G., Kou, L., Yin, S., Han, C., Hu, J., Wan, F., Sun, Y., Wu, J., Li, Y., Huang, J., Xiong, N., Zhang, Z., & Wang, T. (2021). Reactive microglia enhance the transmission of exosomal α-synuclein *via* toll-like receptor 2. Brain : a journal of neurology, 144(7), 2024–2037. https://doi.org/10.1093/brain/awab122

Yang, D., Zhao, D., Ali Shah, S. Z., Wu, W., Lai, M., Zhang, X., Li, J., Guan, Z., Zhao, H., Li, W., Gao, H., Zhou, X., & Yang, L. (2019). The Role of the Gut Microbiota in the Pathogenesis of Parkinson's Disease. *Frontiers in neurology*, *10*, 1155. https://doi.org/10.3389/fneur.2019.01155

Yun, S. P., Kam, T. I., Panicker, N., Kim, S., Oh, Y., Park, J. S., Kwon, S. H., Park, Y. J., Karuppagounder, S. S., Park, H., Kim, S., Oh, N., Kim, N. A., Lee, S., Brahmachari, S., Mao, X., Lee, J. H., Kumar, M., An, D., Kang, S. U., … Ko, H. S. (2018). Block of A1 astrocyte conversion by microglia is neuroprotective in models of Parkinson's disease. *Nature medicine*, *24*(7), 931–938. https://doi.org/10.1038/s41591-018-0051-5

Zhang, Y., Dong, Z., & Song, W. (2020). NLRP3 inflammasome as a novel therapeutic target for Alzheimer's disease. Signal transduction and targeted therapy, 5(1), 37. https://doi.org/10.1038/s41392-020-0145-7

Zimmermann, M., & Brockmann, K. (2022). Blood and Cerebrospinal Fluid Biomarkers of Inflammation in Parkinson's Disease. Journal of Parkinson's disease, 12(s1), S183–S200. https://doi.org/10.3233/JPD-223277

---